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Hepatic necrosis associated with drug-induced hypersensitivity syndrome

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ABSTRACT

Drug-induced hypersensitivity syndrome (DIHS; also known as drug reaction with eosinophilia and systemic symptoms [DRESS]) is a life-threatening condition first described by Chaiken et al. in 1950. It is characterized by extensive mucocutaneous rash; fever; lymphadenopathy; hepatitis; hematological abnormalities; damage to several organs such as kidney, heart, lungs, and pancreas; and possible reactivation of human herpesvirus-6 (HHV-6) or other herpes virus. Rare and severe cases may present hepatic necrosis, and about 15% of them result in death or liver transplantation. A hallmark of this syndrome is the late onset of symptoms after the drug exposure. The most common culprit drugs are the aromatic anticonvulsants (in almost 30% of the cases) and the antibiotics (which in some series represent 20% of the cases). The authors report a case of a 41-year-old female who presented to the emergency department with erythroderma, acute hepatitis, acute pancreatitis and acute renal failure, and was then treated with corticosteroid after the diagnosis of DIHS/DRESS. A specific culprit drug could not confidently be determined due to the presence of multiple drugs used by the patient. The clinical and laboratory outcome was apparently satisfactory, but unexpectedly, on the sixth day of hospitalization, the patient complained of nonspecific malaise, drowsiness, which progressed in a few hours with signs and symptoms of hepatic failure, refractory shock, and death. The autopsy findings showed submassive hepatic necrosis, and the immediate cause of death was attributed to hepatic failure.

Keywords: Liver failure, acute; Massive hepatic necrosis; Drug toxicity; Autopsy.

CASE REPORT

A 41-year-old female patient, previously diagnosed with rheumatoid arthritis, sought the emergency department complaining of pruritus and cutaneous eruption associated with anorexia, fever, and myalgia. Three days after the onset of symptoms, she referred epigastric pain, nausea, vomiting, jaundice, choluria, and her skin started diffuse scaling. She referred urinary tract infection, which was treated with ciprofloxacin until two weeks before the initial symptomatology. On this occasion, she also used scopolamine, dipyrone, and diclofenac. She had been taking prednisone 15 mg/day for the

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last 3 months after methotrexate withdrawal. She denied alcohol consumption, smoking, or recent travel. Physical examination showed a well-looking patient, icteric, hydrated, and febrile. Blood pressure was 80/50 mmHg; pulse rate was 88 regular beats per minute. Dermatological examination showed a diffuse morbilliform exanthematous rash with desquamation compromising face, trunk, abdomen and upper limbs (more than 50% of the body surface). Her face and periorbital area were edematous, and the oral mucous membranes were slightly involved. The liver was tender and enlarged, palpable until 4 cm below the right costal margin. Lungs and cardiac examination were unremarkable. The initial laboratory work-up is shown in Table 1.

Urinalysis sowed proteinuria, occult blood, 21,000 leukocytes/mm^3 and 10,000 erythrocytes/mm^3. Urine culture was negative. Upper abdominal ultrasonography (US) showed an enlarged liver and spleen, slightly distended gall bladder with no calculi images within the biliary system. Abdominal computerized tomography (CT) also showed the presence of lymphadenomegaly in the aortic and iliac chains, with lymph nodes measuring up to 2.2 cm, besides free liquid in the pelvis. Hepatitis A, B, and C and HIV serologies were all negative. Blood cultures were negative for all 6 samples collected.

The analysis of the laboratory tests allowed the conclusion of hepatic, kidney, and pancreatic involvement. Total blood cell count was characterized by leukocytosis, with lymphopenia and monocytosis. These results pointed towards the diagnosis of drug-induced hypersensitivity syndrome (DIHS).

The patient started receiving prednisone 0.5 mg/kg/day and showed a slight clinical improvement until the sixth hospitalization day when she started presenting nonspecific malaise, somnolence, tachycardia, and hypotension. Laboratory tests showed metabolic acidosis and deteriorating liver function. The patient was referred to the intensive care unit but died in 12 hours because of refractory shock.

Retrospectively, in a frozen stored serum sample, serology was positive for immunoglobulin G (IgG) and negative for IgM for cytomegalovirus and Epstein-Bar virus. Human herpes virus-6 (HHV-6) serology, studied by indirect immunofluorescence, was positive for IgG and negative for IgM. The immunoglobulin dosage was within the normal range.

AUTOPSY FINDINGS

External examination showed jaundice and diffuse cutaneous desquamation on the face, trunk, and limbs (Figures 1A, B). Skin microscopy showed dermatitis with scales formation and microscopic skin changes suggestive of drug-induced hypersensitivity reaction in an organization phase. Keratinocytes apoptosis, mild edema of the superficial dermis, and areas of dermal-epidermal cleavage characterized the microscopy of the skin (Figure 1C).

Lymph nodes examination showed lymphoid depletion without eosinophilic infiltration (Figure 1D).

Table 1 – Initial laboratory examination work-up

Exam	Result	RV	Exam	Result	RV
Hemoglobin	13.6	12.3-15.3 g/dL	Sodium	130	136-146 mEq/L
Hematocrit	41.6	36.0-45.0%	Potassium	3.9	3.5-5.0 mEq/L
Leukocytes	15,800	4.4-11.3 × 10^3/mm^3	AST	345	10-31 U/L
Bands	0	1-5%	ALT	425	9-36 U/L
Segmented	84	46-75%	AP	1372	10-100 U/L
Eosinophil	0	1-4%	γGT	1593	2-30 U/L
Basophil	0	0-2.5%	Total bil.	21.3	0.3-1.2 mg/dL
Lymphocyte	5	18-40%	Amylase	781	20-104 U/L
Monocyte	10	2-9%	Lipase	918	< 60 U/L
Platelet	326	150-400 x 10^3/mm^3	INR	1.11	1
Creatinine	2.2	0.4 -1.3 mg/dL	Fibrinogen	573	175-400 mg/dL
Urea	154	10-50 mg/dL	Triglycerides	315	<150 mg/dL
Ionized Ca+	1.06	1.15 -1.35 Mmol/L	Ferritin	1650	22-322 ng/mL

ALT = alanine aminotransferase; AP = Alkalline phosphatase; AST = aspartate aminotransferase; γGT = gamma-glutamyl transferase; INR = international normalization ratio; RV = reference value; Total bil = total bilirubins.

Gross examination of the thoracic cavity disclosed congestion in both lungs. The myocardium showed tiny, yellowish and hardened consistency lesions (Figure 2A), which, on microscopy, corresponded to multiple foci of dystrophic calcification (Figure 2B) and areas of myocardial cell injury in organization (Figure 2C). These histological findings could represent toxic myocardial cells injury in a healing phase.

The abdominal cavity showed the presence of 700 mL of limpid and yellowish ascites. The viscera and fat tissue were diffusely stained by a yellow–gold color, due to bile impregnation. The pancreas showed slight edema weighing 86 g (reference value [RV] = 110 g).

Over the organ, on parenchymal surface cuts, as well in the peripancreatic tissue, numerous foci of fat necrosis were found (Figures 3A, B). These

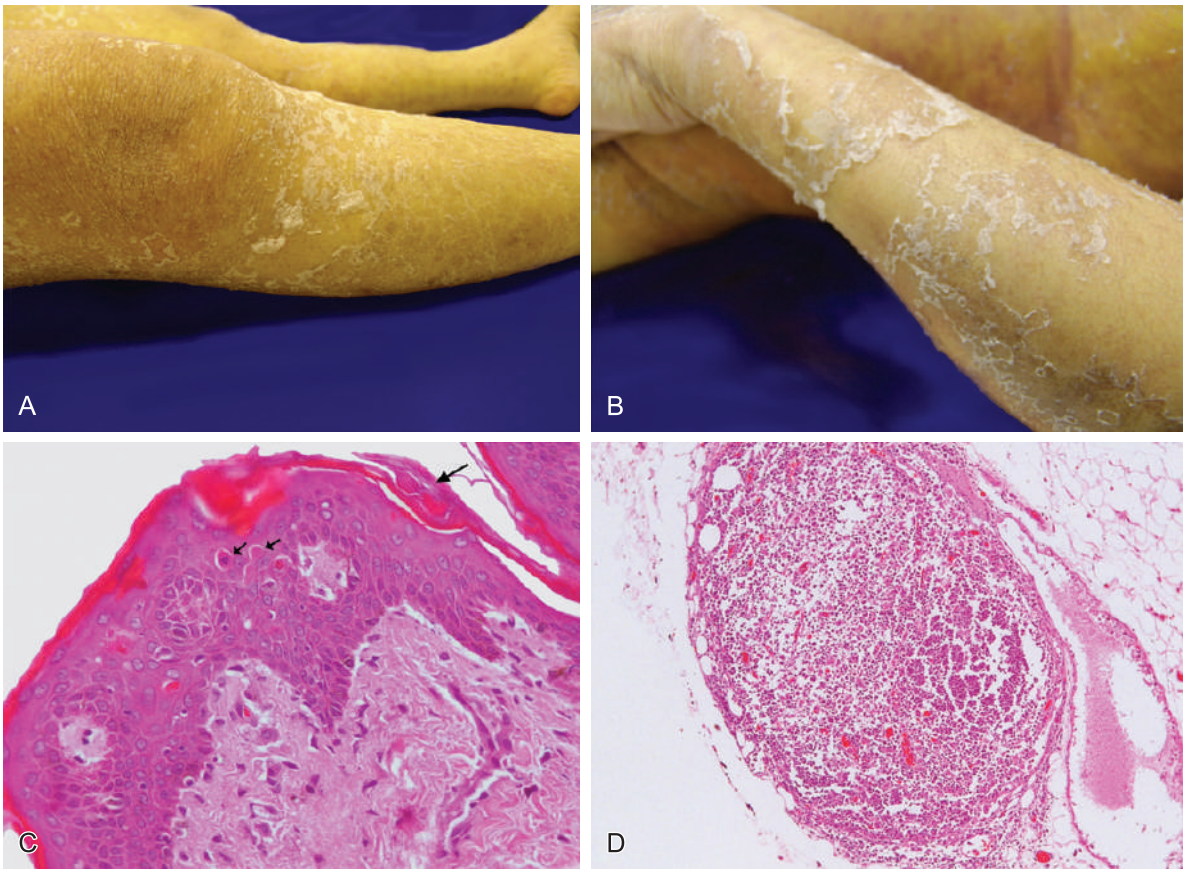

Figure 1 – A and **B -** Gross examination of the body showing diffuse desquamation of the skin; **C -** Photomicrography (H&E) of the skin showing hyperkeratosis and flaking surface (long arrow) and multiple figures of keratinocyte apoptosis (small arrows); **D -** Photomicrography (H&E) of the lymph node showing lymphocyte depletion.

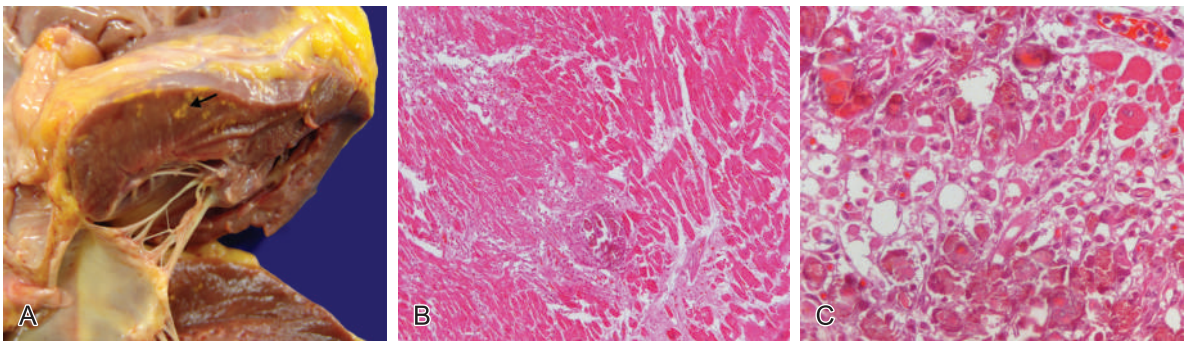

Figure 2 – A - Gross examination of the heart showing the presence of yellowish nodules (arrow); **B -** Photomicrography (H&E) of the myocardium showing multiple foci of dystrophic calcification; **C -** Photomicrography (H&E) of the myocardium showing areas of myocardial cell injury in organization.

findings confirmed the diagnosis of acute edematous pancreatitis on microscopy (Figures 3C, D).

The liver had a yellowish color, was of soft consistency, and weighed 1735 g (RV range = 1140-1450 g). The hepatic cut (Figure 4A) surface showed multiple bleeding points on the topography of the center-lobular hepatic vein, which was represented by extensive areas of necrosis and loss of the trabeculation on microscopic examination (Figures 4B-D).

The spleen was enlarged and congested, weighing of 549 g (RV = 112 g) showing acute splenitis (Figure 5A). Gross examination detected wedge areas of yellowish and soft consistency tissue (Figure 5B) that on microscopy corresponded to ischemic necrosis (Figure 5C). Additional findings included generalized visceral congestion; moderate esophagitis; gastritis; small mucosal bleeding points scattered in the cecum and ascending colon; uterine fibroids and corpus luteum hemorrhagic cysts in the ovary; and lipid deposition in the abdominal aorta. Remaining organs and tissues showed no significant alterations on gross and microscopic examination.

DISCUSSION

DIHS, also known as drug reaction with eosinophilia and systemic symptoms (DRESS), is a life-threatening condition, which, in its complete form, is characterized by mucocutaneous rash, fever, lymphadenopathy, hepatitis, hematologic abnormalities, and damage to several organs such as kidney, heart, lungs, and pancreas.[1] There is a trend to consider DIHS as the precise denomination for this syndrome. A hallmark of this syndrome is its late onset after the culprit drug exposure, unlike other drug reactions, which occur earlier after drug exposure, like the acute generalized erythematous pustulosis and Stevens-Johnson syndrome/toxic epidermal necrolysis.[2] This latency is fairly variable in the literature, described as being between 2 weeks and 3 months.[1-3,4] Um et al.[5] reported 6 cases in a series of 38 patients, and Ang et al. reported 3 cases in a series of 27,[6] where this latency period was less than 1 week. This small latency was correlated to antibiotics and NSAIDs. The syndrome may develop after the very first use of the drug and after its re-administration.[1]

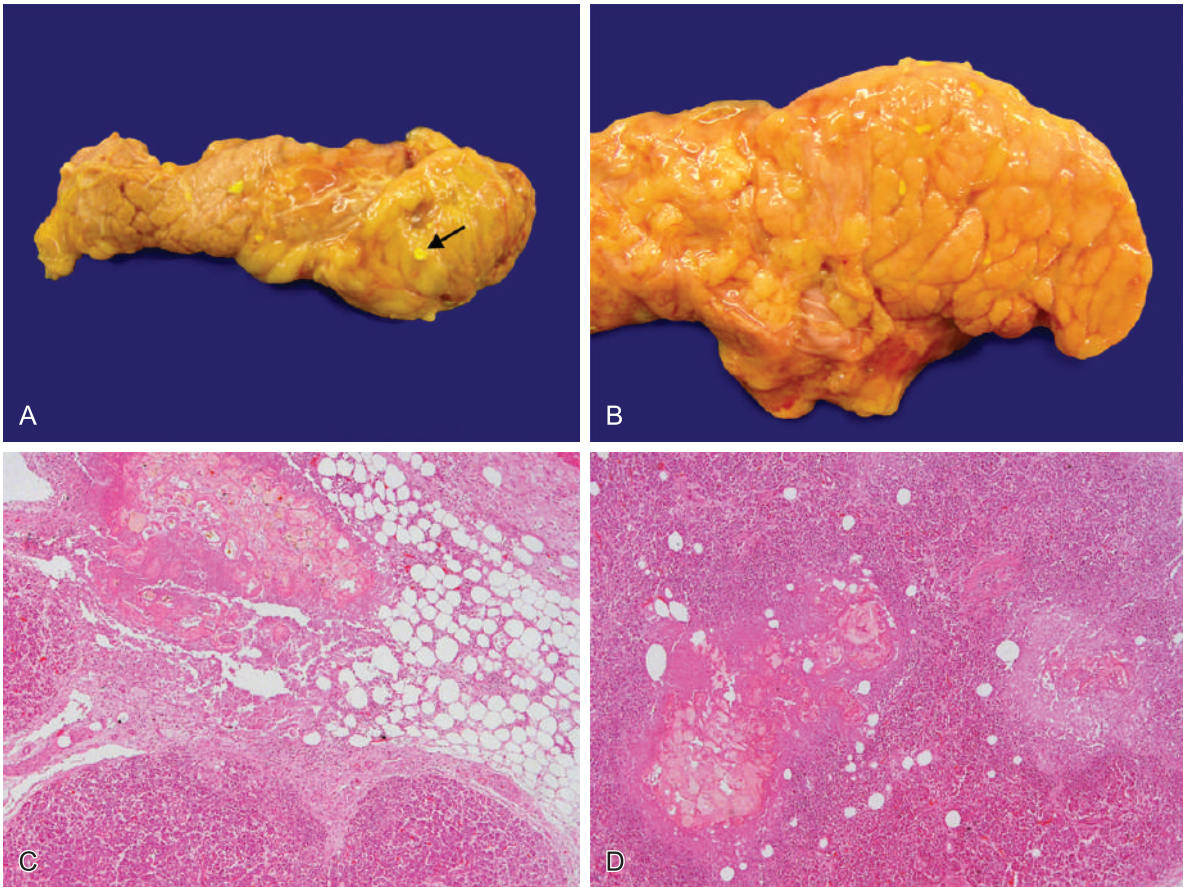

Figure 3 – A - Gross examination of the pancreas showing acute edematous pancreatitis with foci of fat necrosis on the surface of the organ (arrow) and in the cut surface of the parenchyma in **B**; **C** and **D -** Photomicrography (H&E) of the pancreas depicting pancreatic and peripancreatic fat necrosis.

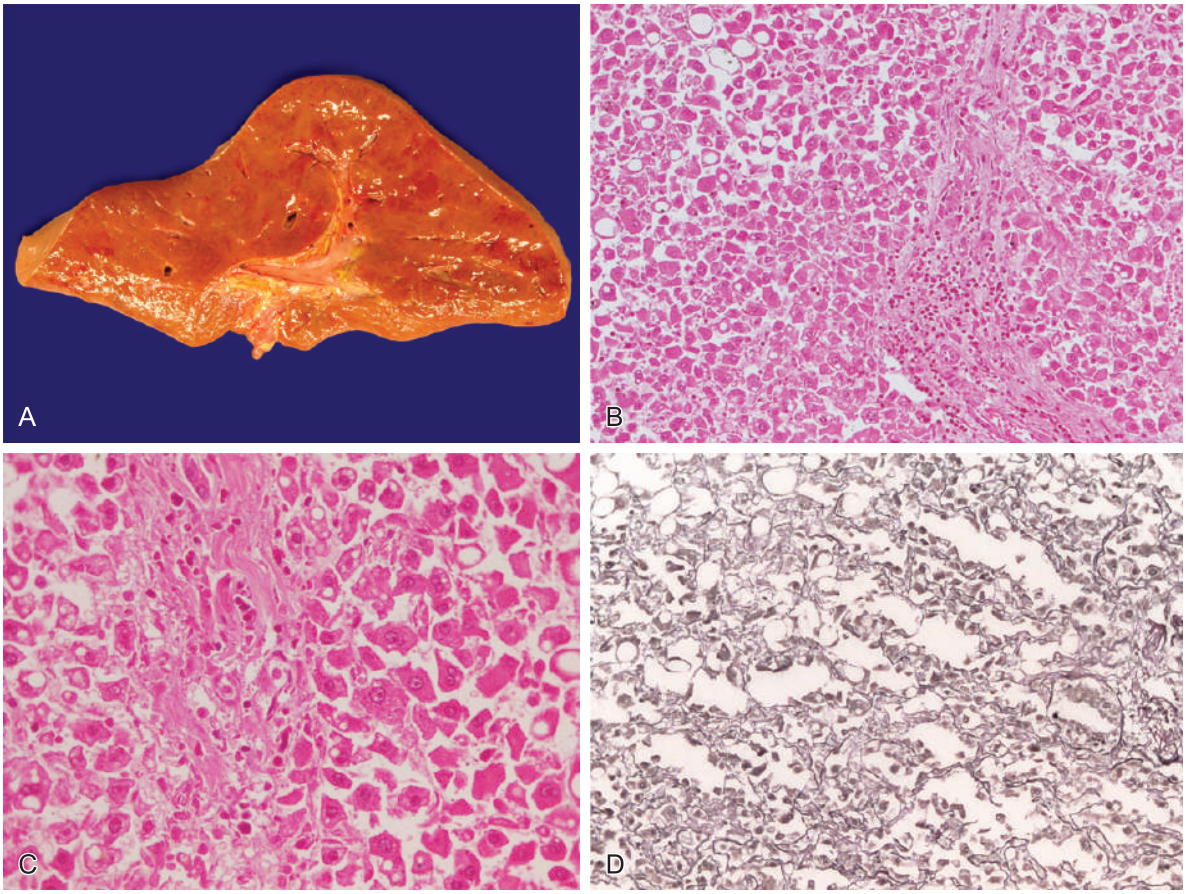

Figure 4 – A - Gross examination of the hepatic cut surface showing yellowish and hemorrhagic areas; **B** and **C** - Photomicrography (H&E) of the liver showing hepatic necrosis; **D** - Photomicrography of the liver (immunohistochemical staining for reticulin) showing the loss of the normal liver parenchyma trabeculation.

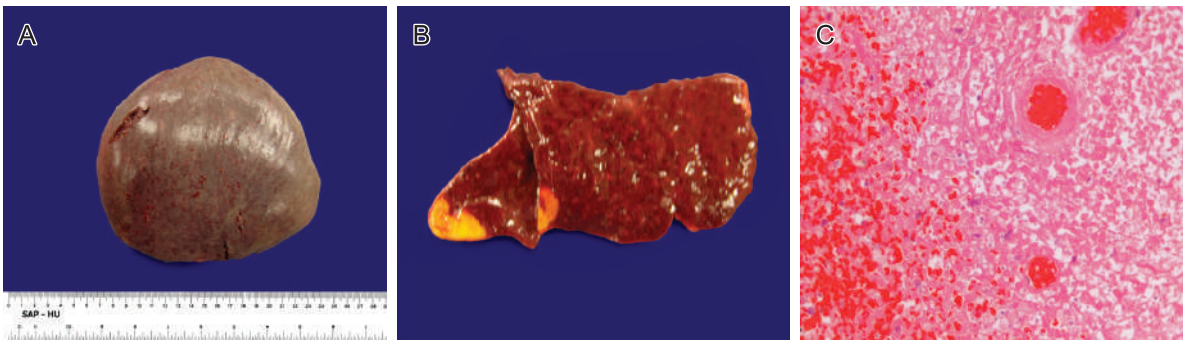

Figure 5 – A - Gross appearance of the enlarged spleen; **B -** Gross examination of the splenic cut surface showing acute splenitis, and ischemic wedge yellowish areas; **C -** Photomicrography (H&E) of the spleen showing ischemic necrosis.

First described by Chaiken et al. in 1950,[7] DIHS is an unpredictable reaction with an incidence ranging from 1 in 1000 to 1 in 10,000 patients.[5,8,9] It occurs more frequently in adults, has no gender predominance[1], and is not related to dose or serum concentration of the offending drug.[10] Mortality is observed in 10-20% of the cases, especially those related to advanced age, renal impairment, and severe hepatic injury.[1,11]

The exact mechanism by which the drug triggers the syndrome remains to be fully determined. Pathogenic data are more consistent with aromatic anticonvulsants as culprit drugs, but there is a trend to accept the same mechanisms when other dugs are involved. The ethiopathopenesis of DIHS/DRESS comprises: a) deficiency of the epoxide hydroxylase enzyme that detoxifies drug metabolites (in this case, the accumulation of arene oxides promotes direct cellular toxicity and/or triggers an immune response); b) reactivation of herpes virus family; and c) genetic predisposition (abnormal detoxification of some drugs is thought to be inherited in autosomic co-dominant fashion[12] and familial cases have been reported

and certain human leukocyte antigen (HLA) alleles were shown to be closely associated with cutaneous reactions).[1,5,13] Reactivation of HHV-6 or other herpes virus can be evidenced by increases in the title of IgG anti HHV-6 after the second week of the rash onset by the maintenance of elevated IgM levels during the course of reaction[14] or by detection of viral genome by protein chain reaction (PCR) in the blood. The latter, when absent, raises the suspicion of other sites for the viral reactivation, such as the spleen or lymph nodes.[11,15] The role of herpesvirus reactivation in the syndrome seems to be related to an immune response elicited by the drug, activating macrophages, lymphocytes, and cytokine release. The virus, housed in these cells, would therefore be jointly reactivated.[16] Shiohara et al. proposed that the clinical symptoms during DIHS/DRESS do not only seem to be mediated by the expansion of drug-specific T cells, but also by antiviral T cells cross-reacting with drugs.[1,16] Depending on the extent of macrophage activation and the cytokine storm, a hemophagocytic syndrome may be elicited. In this case, hyperferritinemia may reflect this hypercytokinemia.[17] In this case report, viral serologic work-up was undertaken precociously, at the beginning of the syndrome. These serologies could not be repeated because of the unfavorable outcome; therefore it was not possible to demonstrate the viral reactivation.

A recent review of literature concerning drugs related to DIHS/DRESS found 44 different drugs related to 172 cases in the period from 1997 until 2009.[18] The most common drugs involved in the pathogenesis of DIHS/DRESS are the aromatic anticonvulsants (almost 30% of the cases) such as phenytoin, carbamazepine, phenobarbital, lamotrigine, and primidone. However, other drugs are also well established as potential triggers, such as allopurinol, minocycline, calcium channel blockers, angiotensin converting enzymes inhibitors, beta-blockers, dapsone, terbinafine, NSAIDs, anti-retroviral drugs, quinine,[19] sulfasalazine,[20] bupropion,[21] ranitidine, methimazole, propylthiouracil, azathioprine, and biologic agents.[1,22] Antibiotics are being fully associated with DIHS/DRESS, after recent reports where they were involved in 20% of cases.[5] Among them are trimethoprin-sulfamethoxazole, β-lactams, quinolones, and sulfonamide.[1,3,5,11] In the case reported here, we observed the full clinical picture described for DIHS, precociously raising the suspicion. The latency period between the initial symptoms and the drugs' exposure was 2 weeks, in accordance to the diagnostic requirements. In this case, it became difficult to confidently identify the culprit drug due to the presence of multiple drugs. Even so, we raised the suspicion that ciprofloxacin was the most probably offending drug, once this drug has already been reported in the literature presenting similar clinical picture.[23] Ciprofloxacin has been also recognized as a drug capable of causing hepatic injury. A study of cases from Drug-Induced Liver Injury Network (DILIN) from September 2004 to January 2010 found 12 cases (out of 679), related to fluoroquinolones hepatotoxicity. In this study,[24] the average time between the drug and the onset of symptoms was 4 days (range 1-39 days); one of these cases died because of acute hepatic failure. Ciprofloxacin was the drug in 6 of these cases.[24]

Fever as high as 38-40 °C is the most common symptom occurring in 90-100%[25] of cases followed in frequency (90%)[25] by involvement of the skin, which is characterized by a morbilliform rash, which is indistinguishable, in most cases, from other drug reactions. The face, upper trunk, and upper extremities are initially affected, with subsequent progression to the lower limbs. Swelling of the face, with marked periorbital involvement may be a diagnostic clue and is present in 25% of cases.[25] The maculopapular eruption later becomes infiltrated, and vesicles are infrequent. Over time, the rash becomes purplish and ends with scaling.[1,26] Another form of presentation is as exfoliative dermatitis, also associated with mucosal involvement.[27] A skin biopsy does not establish the diagnosis but can assist in its confirmation, showing lymphocytic infiltration of the papillary dermis that may contain eosinophils and perivascular inflammatory infiltrate.[6,28] The patient of this case report presented high grade fever from the onset until the end. Her cutaneous involvement was represented by generalized erythema (exanthematous rash) with scaling and facial edema.

Lymphadenopathy may be localized or generalized and occurs in 50-75% of the cases.[5,25] The lymph nodes may present a benign pattern of lymphoid hyperplasia or a standard pseudolymphomatous aspect with disruption of normal architecture of the organ.[1,29] In this case report, the lymph node involvement was detected by CT images and confirmed at autopsy. The histology was characterized by lymphocitary depletion, contrary to what has been described hitherto. This histological difference may be explained by the chronic use of corticosteroid and other immunosuppressant drugs used in the past.

Hematologic abnormalities occur in up to 50% of cases,[25] and are characterized by marked leukocytosis (up to 50,000/mm^3), eosinophilia (30% of cases), monocytosis, and lymphopenia. Atypical lymphocytes are not rare, usually appearing in the onset of symptoms,[1,29] which is different from the

eosinophilia that is observed 1-2 weeks later.[30] More rarely, thrombocytopenia, leukopenia, or even pancytopenia may be observed.[5] Hemophagocytic syndrome has been reported in the course of DIHS/DRESS, usually after the second week of the drug eruption.

After lymphadenopathy, the most common visceral involvement refers to the liver (50-60% of patients).[25] More commonly, hepatic injury is represented by isolated elevation of hepatic transaminases, which is usually anicteric.[1,29] Severe cases may present focal or spread hepatic necrosis, characterized by alanine transaminase (ALT) elevation of 10 times the reference value or by acute liver failure with coagulopathy and encephalopathy. This worse outcome is mostly observed in women in the fourth decade of life. Apparently it does not show a change in course with immunosuppressants. About 15% of cases result in death or liver transplantation.[1,30] Splenomegaly is frequently observed accompanying hepatomegaly.[30] The patient of this case report was a middle-aged woman who, after an initial apparent clinical improvement, developed a dramatic hepatic failure rapidly evolving to death. Splenomegaly was also present in this case. The autopsy found a submassive hepatic necrosis.

The renal involvement occurs in approximately 11-15.8% of the cases,[5,25] which is outlined by an increase in serum urea and creatinine, and sometimes by hematuria proteinuria or eosinophiluria.[5,30] The kidney histology generally reveals tubulointerstitial nephritis and granulomatous necrotizing angiitis.[6,31] On admission laboratory tests, the patient of this report showed results being compatible with acute renal failure and an unquantified proteinuria on the urinalysis. The renal histology of the case reported here, was more compatible with a final event (acute tubular necrosis), but we assume the initial renal impairment, as due to DIHS/DRESS, once there was no other reason for the renal insufficiency.

Myocardial involvement is fairly variable, ranging between asymptomatic cases and heart failure, chest pain, dyspnea, and hypotension. The most severe presentation is represented by the acute necrotizing eosinophilic cardiogenic shock, implicated with drug hypersensitivity, which histology shows eosinophilic and lymphocytic infiltration with extensive myocardial cell necrosis.[32] When symptomatic, the echocardiogram may show reduced left ventricular ejection fraction, and the chest x-ray shows an enlarged cardiac silhouette. The electrocardiogram is nonspecific with changes in the ST segment or T wave abnormalities, conduction delay, sinus tachycardia, and ventricular arrhythmias. The echocardiogram may show systolic dysfunction and occasional pericardial effusion. Myocardial necrosis biomarkers may show elevation of creatine kinase-MB fraction and in severe cases of eosinophilic myocarditis troponin-I may also be raised. Sudden cardiac death has been reported.[3,30,33,34] In this case report, the autopsy findings represented by the yellowish nodules and the histologic demonstration of myocardiocyte injury were interpreted as a myocardial lesion of the DIHS/DRESS syndrome.

Pancreatitis occurring in association with DIHS/DRESS is rare; generally it occurs as a late consequence of multiorgan failure.[29] Roquin et al. reported a case of pancreatitis associated with DIHS/DRESS in the early stage of the disease. Criado et al, reported another case of a young woman who developed DHIS/DRES after using carbamazepin, presenting acute pancreatitis with a fatal outcome.[35] In the case reported here the elevation of lipase and amylase serum determinations were present at admission. The abdominal CT images did not elucidate a pancreatitis diagnosis, but the autopsy findings were indisputable.

Diagnosis of the syndrome is sometimes challenging due to incomplete clinical presentation. Therefore Bocquet et al. first proposed diagnostic criteria,[29] requiring eosinophilia and/or lymphocytic atypia for the diagnosis. In the cases where this criterion was not present, like DIHS, diagnosis could not be considered definite or typical. Hence, the Japanese study group (SCR-J) adopted other criteria in which eosinophilia was not a mandatory criterion, but the HHV-6 replication requirement became an obstacle for its wide use. The European group, RegiSCAR, more recently proposed a third diagnostic criteria published by Kardaun et al., best suiting up the different institutions and the needs for diagnosis.[36] Our case meets the diagnostic criteria for the SCR-J as atypical DIHS because of the lack of demonstration of HHV-6 reactivation (for the reasons we discussed above). The RegiSCAR score of this case report was 5, namely: fever = 0/lymphadenomegaly = 1/skin rash extent suggesting DRESS = 2/organ involvement = 2 (liver, heart, pancreas). Unfortunately the criterion “other potential causes” could not be filled because of the lack of ANA testing. ANA was not tested because the patient had a history of rheumatoid arthritis and its positivity could be misinterpreted. Despite the abnormal renal function shown in Table 1, we did not consider the kidney in the list of involved organs because of the lack of microscopic findings at autopsy. Regardless

of the number of involved organs, RegiSCAR criteria permit a maximum score of 2 for this item.

The exclusion of other serious infections, neoplastic diseases, autoimmune, or connective tissue diseases, is advisable for the accurate diagnosis DIHS/DRESS.[1,11,37]

Awareness, early recognition of the diagnosis of DIHS/DRESS and withdrawal of the offending drug are the most important steps toward clinical improvement.[1,16] Systemic corticosteroids (prednisone or methylprednisolone) have been widely used in the treatment of the syndrome. The dose can be reduced after clinical and laboratory improvement, and slow-tapered over 6-8 weeks afterwards, in order to prevent recurrence.[1,3,16] Intravenous immunoglobulin (IVIG), plasmapheresis, or a combination of these therapies can be used in the case of worsening symptoms.[16,38,39] A consensus of experts on the therapeutic management of DIHS/DRESS was published in 2010.[40]

This case was treated with a systemic corticosteroid, which resulted in cutaneous improvement and apparent improvement of liver enzymes, total bilirubins, renal function, and pancreatic enzymes. Clinical worsening was sudden and overwhelming, giving no chance for other therapeutic options.

CONCLUSION

This case report illustrates the potential severity of DIHS/DRESS, even in cases where control of the disease is supposedly achieved. We call attention to the diagnosis recognition and awareness of a possible fatal outcome.

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